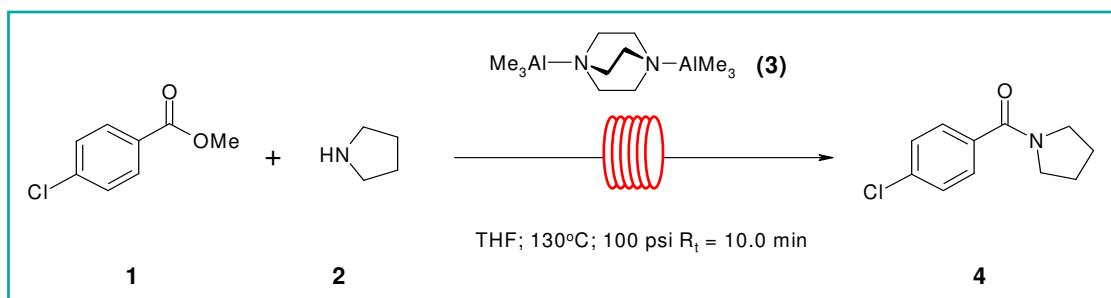


FlowSyn™ Application Note 28: Amide Bond Formation in Flow using DABAL-Me₃



Introduction:

Amide bond formation is an important reaction in organic synthesis that constitutes a cornerstone of medicinal and combinatorial chemistry. However, an increasing number of convenient and efficient reagents for forming amide bonds have become restricted due to concerns about their stability or toxicity. Interest remains therefore in identifying new coupling reagents that are both convenient to use and effective for a range of starting acids and amines.

The direct amidation of esters with amines in the presence of trimethylaluminium constitutes an attractive synthetic strategy that has previously been demonstrated to proceed rapidly at elevated temperatures under continuous flow through conditions.¹ However, trimethylaluminium is an extremely moisture sensitive reagent that remains pyrophoric even as a solution in toluene and is hazardous to use.

More recently, the complex between trimethylaluminium and DABCO has been reported as a more benign alternative.^{2,3} The DABAL-Me₃ complex is a white solid that is soluble in a range of organic solvents such as THF and toluene and can be handled under a local inert atmosphere without the need for a glove box or specialised Schlenk techniques.

- In this Application Note, since the rate of the amidation reaction is extremely slow at room temperature, all the reagents are conveniently pre-mixed.
- The FlowSyn was fitted with large sample loops (20ml) to avoid the need to pass any reagents through the pump heads.
- Continuous processing can be achieved at scale by alternating between both flow channels, refilling the 'off-line' sample loop when it has been emptied.
- The reaction product was readily isolated in high purity by organic extraction from an acidic aqueous phase (pH ~1), followed by re-crystallisation from hexane.
- Throughput can be increased by utilising larger sample loops. (Sample loops up to 50ml in volume are also available.)

Method:

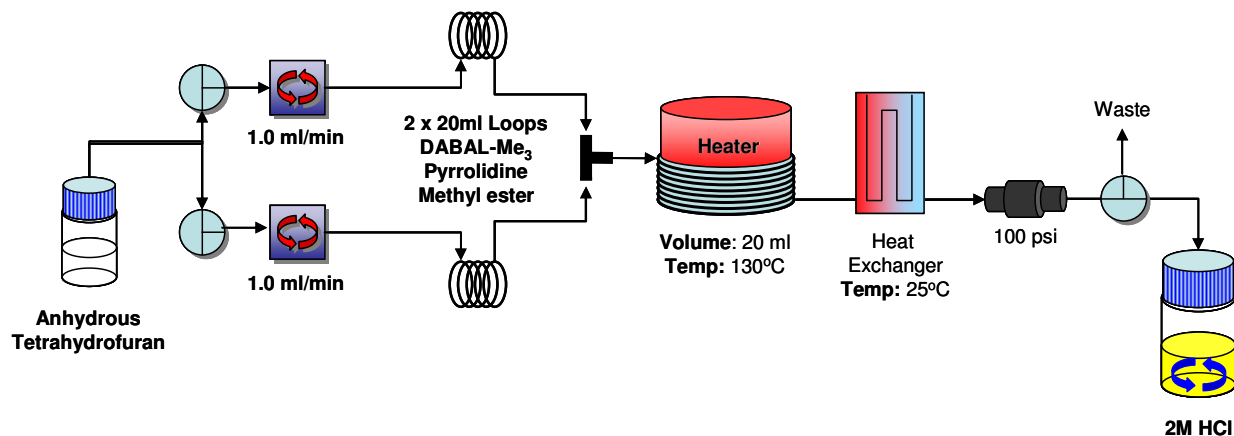
System solvent: Tetrahydrofuran (anhydrous).

Sample Loops A&B: Methyl 4-chlorobenzoate (4.42g, 25.9mmol), DABAL-Me₃ (5.31g, 20.7mmol) and pyrrolidine (2.55ml, 31.1mmol) diluted to 40ml in tetrahydrofuran (anhydrous). (Pre-mixed and Schlenk filtered through oven-dried celite.)

The FlowSyn was fitted with a 20ml stainless steel coil reactor and a 100psi fixed back pressure regulator.

The reactor outflow was directed into a 250ml collection bottle containing 2M hydrochloric acid (100ml) that was continually stirred using a magnetic stirrer.

Schematic:



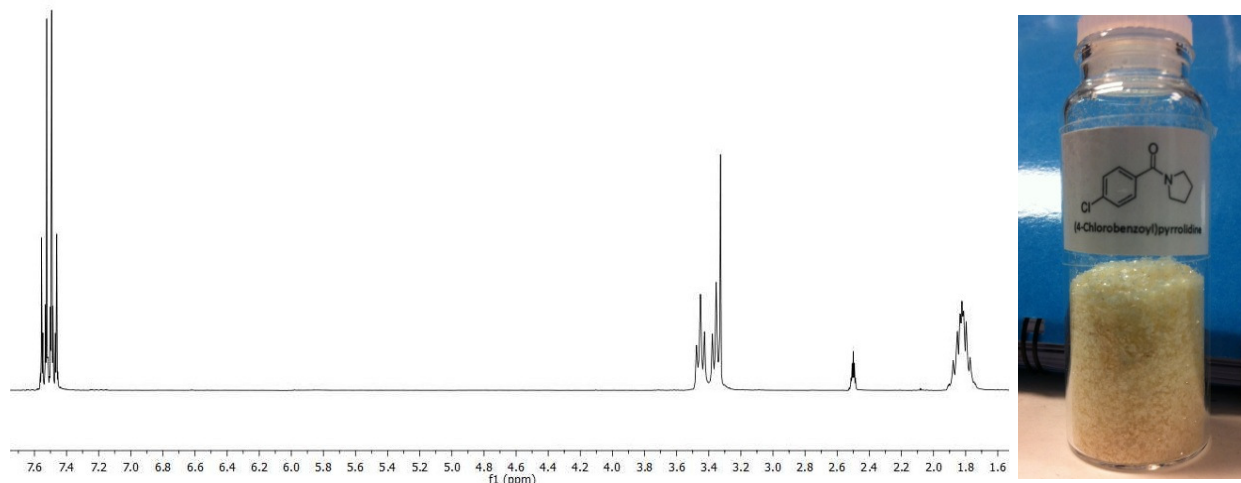
System Configuration			
RH reactor:		LH reactor:	
Type:	Coil	Type:	None
Material:	Stainless Steel	Material:	N/A
Volume:	20.0 ml	Volume:	N/A
Max Temp:	260°C	Max Temp:	150°C
System Dead Volume:	0.60 ml	Heat Exchanger:	Yes
Minimum Pressure:	5 bar	Pump Start Delay:	10 s
Maximum Pressure:	30 bar	Pressure Units:	bar
Pressure Threshold:	Off	Equil. Flow Rate:	0.5 ml/min
Wash Flow Rate:	5.0 ml/min	Loop Volume:	20 ml

Auto Set Up			
Inlet A:	Loop	Coil Residence Time:	00:10:00
Inlet B:	Loop	Column Residence Time:	00:00:00
Volume A:	20 ml	Total Flow Rate:	2.0 ml/min
Volume B:	20 ml	Pre Collect:	0.00 ml
A:B Ratio:	[1:1]	Post Collect:	30.00 ml
Coil Temp:	130C	Final Wash:	0.00 ml
Column Temp:	25C	Intermediate Wash:	0.00 ml

Throughput = 14.7 g/h

The collected material was extracted with dichloromethane (3 × 30ml) and dried with MgSO₄. The solvent removed *in vacuo* to afford crude **4** as pale yellow solid (4.91g, 91%). The crude material could be re-crystallised from hexane to give **4** as pale yellow flakes (mp 73 - 75°C).

¹H-NMR (DMSO-*d*₆; 400Hz): 1.75 - 1.91 (m, 4H), 3.35 (t, *J* = 12.0 Hz, 2H), 3.45 (t, *J* = 12.0 Hz, 2H), 7.54 - 7.56 (m, 5H)



Risk Assessment and Hazards:

General: The instrument should be located in an adequately ventilated instrument enclosure or a laboratory fume cupboard with the perspex safety shield in place, and only be operated by a technically competent and experienced scientist wearing safety spectacles, a protective laboratory coat and gloves. The flow reactor operates at elevated temperature and high pressure, therefore ensure cabinet doors remain closed during operation.

Spillages: Isolate instrument from electrical supply. Small spillages on the equipment may be removed with aqueous isopropanol. Larger spillages should be diluted with water and washed to drain or absorbed using spill cushions. FlowSyn is fitted with a PTFE coated containment tray.

Reagent	CAS Number	Hazards
Methyl-4-Chlorobenzoate	1126-46-1	None
Pyrrolidine	123-75-1	Flammable, Irritant
DABAL-Me ₃	137203-34-0	Contact with water liberates flammable gases
THF	109-99-9	Flammable, Irritant

Any reagents accidentally coming into contact with the skin should be removed immediately by washing with soapy water. Contamination of the eyes should be treated by copious irrigation with saline before seeking medical attention.

References

1. T. Gustafsson, F. Pontén, P. H. Seeberger, *Chem. Commun.*, **2008**, 1100.
2. a) N. Dubois, D. Glynn, T. McNally, B. Rhodes, S. Woodward, D. J. Irvine, C. Dodds, *Tetrahedron*, **2013**, 69, 9890. b) D. Glynn, D. Bernier, S. Woodward, *Tetrahedron Lett.* **2008**, 49, 5687. c) A. Novak, L. D. Humphreys, M. D. Walker, S. Woodward, *Tetrahedron Lett.* **2006**, 47, 5767.
3. S. Woodward, D. S. Lee, <http://youtube/RfeaffoWajc>

Acknowledgements

This study was undertaken by Darren Lee in the laboratory of Professor Simon Woodward, Nottingham University, University Park, NG7 2RD, UK (27-05-2014).